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Bipolar disorder and addictions – the elephant in the room

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Declaration of interests:

Dr Paul Stokes has received support for research, expenses to attend conferences and fees for lecturing and consultancy work (including attending an advisory board) from life sciences companies including Corcept Therapeutics, Indivior and Liva Nova. Dr Stokes is a consultant psychiatrist within a tertiary level specialist service and a specialist consultant advisor in mood disorders for the UK Civil Aviation Authority. Dr Kalk has received funding for educational activities, including travel expenses, and research expenses during her PhD (2010-2013) from GlaxoSmithKline, as her PhD was funded by a Wellcome Trust GSK Translational Medicine Training Fellowship. Prof Allan Young has been commissioned to give lectures and is on advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders. Prof Young was the lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study. Prof Young has been involved in investigator initiated studies from AZ, Eli Lilly, Lundbeck and Wyeth. Prof Young has been awarded research grants from: NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). This report represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Summary:

Addictions are highly prevalent in bipolar disorder and greatly impact on clinical outcomes. In this editorial, we review the evidence that addictions are a key challenge in bipolar disorder, examine putative neurobiological mechanisms, and reflect on the limited clinical trial evidence base with suggestions for treatment strategies and further developments.

Editorial:

Bipolar disorder is one of the most challenging mental health disorders to assess and treat and a key challenge is the very high rates of addiction co-morbidities experienced by people with bipolar disorder. The increased prevalence of addictions in bipolar disorder is demonstrated by the recent United States National Epidemiologic Survey on Alcohol and Related Conditions which found that people with bipolar I disorder have a 5.8 times increased lifetime risk of a substance use disorder diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. This risk was still 2.3 times increased even after adjusting for other psychiatric co-morbidities (1). Studies in the United Kingdom also reflect the increased risk of addictions in bipolar disorder with 48% and 44% of people with bipolar disorder experiencing a lifetime history of alcohol and substance abuse respectively (2). Bipolar disorder has one of the highest rates of cigarette smoking of any mental health disorder and the lowest rate of smoking cessation (3). Increased rates of behavioral addictions, such as gambling disorder (4), have also been identified in bipolar disorder and approximately 1 in 10 people with bipolar disorder may have a moderate to severe lifetime risk of problem gambling (4). Addiction co-morbidity in bipolar disorder is important as it greatly impacts on clinical outcomes. For example, addiction co-morbidity in bipolar disorder is associated with more severe manic episodes, and increased risks of violence, suicide and relapse (5, 6). Despite their greater needs and increased risk, people with bipolar disorder and addiction co-morbidity often struggle to access secondary mental health services (7).

Why are addictions so prevalent in bipolar disorder?

The association between bipolar disorder and addictions raises the question: why are people with bipolar disorder at increased risk of addictions? There are several potential mechanisms. The first is that people with bipolar disorder “self-medicate” with alcohol or drugs to alleviate mood episodes. However only 25% of people with bipolar disorder increase their use of alcohol during a manic episode and most don’t change their use during a depressive episode (8). Indeed, people with bipolar disorder and addiction co-morbidities are no different to people with substance use disorder in experiencing increased substance sensitivity or sensation seeking, and in using substances to achieve a sense of euphoria or to alleviate mood and anxiety

symptoms irrespective of current mood episode. They also report similar motivations for substance use as the general population (9).

The second potential mechanism is a shared neurobiology between bipolar disorder and addictions which means that people with bipolar disorder are at risk of addictions. Indeed, the prospective Zurich cohort study showed that manic symptoms or a diagnosis of bipolar II disorder was associated with a greatly increased risk of developing alcohol or benzodiazepine dependence over twenty years (10). Certainly there is evidence that young men who report high rates of hypomanic symptoms, and may be at risk of developing bipolar disorder, experience similar low level behavioral responses to alcohol as is found in those with a family history of alcohol dependence (11). Addiction co-morbidities in bipolar disorder are likely to be mediated by the involvement of a number of neurotransmitter systems. Much of the focus of addiction research has been on the dopamine neurotransmitter system and it is likely that vulnerability to addictions in bipolar disorder may be mediated, at least in part, through dopaminergic dysregulation. However, the evidence for this is limited by a lack of studies of the dopamine system in people with bipolar disorder and addiction comorbidity (12). Anxiety disorders are also highly prevalent in bipolar disorder and so there is also the possibility that people with bipolar disorder use alcohol or other substances to alleviate anxiety symptoms perhaps generated by GABA-A receptor dysregulation previously reported in anxiety disorders (13).

Treatment approaches

How to do we best treat people with bipolar disorder and co-morbid addictions? The first step is to ensure that co-morbid addictions are adequately identified in people with bipolar disorder. National Institute for Health and Care Excellence guidelines recommend that all patients who disclose substance use are asked about quantity, frequency and pattern of use, route of administration and duration of current level of use (14). It is also important to establish whether criteria for substance dependence is met as this will greatly influence clinical management (14). We would suggest that a history of behavioural addictions such as gambling, sexual and shopping addictions is also taken. Frequent re-assessment of substance use and behavioural addictions is recommended especially following a change in mental state (15). Once addiction co-morbidity has been identified the intensity of intervention will depend on the severity of the problem identified and resources available locally, but joint working with expert addictions services is recommended to achieve the best outcomes (7). It is important to note that addiction services are rarely commissioned to provide psychiatric care and so secondary care mental health services should lead treatment and people with bipolar disorder should not be excluded from these services because of addiction co-morbidity (7). Clinicians should also develop care plans that consider the potential for greater mood instability, higher risks of self-

harm, and poorer medication adherence found in people with bipolar disorder with addictions co-morbidities.

Pharmacological management

The pharmacological management of bipolar disorder with addiction co-morbidities is complicated by a lack of good quality, placebo controlled, randomized control trials (RCTs). This may partly be due to pharmaceutical industry sponsored trials excluding people with bipolar disorder and co-morbid addictions. The evidence that does exist is based on a relatively small number of RCTs which typically assess the effects of interventions in less than thirty participants over a twelve-week period. Several RCT's have investigated the effects of mood stabilizers on substance use and mood scores. Although we are not aware of any studies that have examined the effect of lithium in people with bipolar disorder and alcohol dependence, a large multicenter trial of lithium in alcohol dependent people with a history of depression found no improvement in alcohol consumption or mood scores (16). Another study found that sodium valproate in addition to lithium and psychosocial interventions improved alcohol consumption but not mood scores in people with bipolar disorder and alcohol dependence (17). Turning to bipolar disorder with substance use disorder co-morbidity, a large trial that compared the effectiveness of lithium and valproate compared to lithium alone failed due to lack of adherence and non-response to acute treatment (18). Lamotrigine has been found to improve the amount spent on cocaine but not mood scores in people with bipolar disorder and cocaine dependence (19) and, in a small RCT, lithium has been found to be effective in reducing gambling behaviour and mood instability in pathological gamblers with bipolar disorder (20).

There are surprisingly few studies of the effectiveness of antipsychotic medication in people with bipolar disorder and co-morbid addictions. Those studies that are available have examined the effectiveness of adding quetiapine to mood stabilizers for alcohol use disorder co-morbidity and have shown that it is largely ineffective in improving either alcohol consumption or mood measures (21, 22). Two small pilot RCTs have investigated the effectiveness of adjunctive acamprosate or naltrexone in alcohol dependent people with bipolar disorder. Neither found improvements in alcohol consumption or mood scores (23, 24), although naltrexone was associated at a trend significance level with fewer drinking days and lower craving scores, and both medications were safe, well-tolerated and did not destabilize mood. Naltrexone is recommended by the British Association for Psychopharmacology treatment guidelines to help people with bipolar disorder to reduce their alcohol consumption and acamprosate is then recommended if naltrexone has not been effective in supporting abstinence (15).

Limitations

There are several limitations which constrain our understanding of addiction co-morbidity in bipolar disorder and how best to provide treatment. Most of the prevalence data originates from developed countries, particularly the USA, and there is a real need for co-morbidity prevalence data from developing countries. Given the importance of addictions in bipolar disorder, there are also surprisingly few studies which have investigated neurobiological mechanisms which mediate addictions co-morbidity. There have also been few well powered RCTs which have investigated the effectiveness of pharmacological treatments for bipolar disorder with addiction co-morbidity and the lack of an evidence base is a real challenge in determining best treatment practice.

Conclusions

Addictions are highly prevalent in bipolar disorder and impact on clinical outcomes and risk profiles. The reasons why people with bipolar disorder are at high risk of addiction remain unknown and require further investigation but may be mediated by shared neurobiological mechanisms. Treating addictions in bipolar disorder requires an inclusive, comprehensive approach which supports the identification of addiction co-morbidity in bipolar disorder and the development of care plans to minimize risks. There is an urgent need for well powered placebo controlled RCTs in this area and, as addictions are so prevalent in bipolar disorder, we suggest that excluding people with bipolar disorder with a history of addictions from clinical trials significantly limits the generalizability of findings to the 'real life' bipolar disorder population.

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